Evaluating the contribution of *APOBEC3G* haplotypes on influencing HIV infection in a Zimbabwean paediatric population

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Background. Apolipoprotein B mRNA-editing catalytic polypeptide like-3G (*APOBEC3G*) is an antiviral enzyme that reduces viral fitness by introducing uracil to thymidine hypermutations in viral genomes. Thus, polymorphisms in the *APOBEC3G* gene have been implicated in differential outcomes of HIV infection and disease progression. However, there is insufficient evidence on the role of *APOBEC3G* gene variants on HIV infection, especially in African populations. This study therefore describes polymorphisms in the *APOBEC3G* gene in a Zimbabwean paediatric population and evaluates their effects on susceptibility to HIV infection among children born to HIV-infected mothers.

Methods. A total of 104 children aged between 7 and 9 years, comprising 68 perinatally exposed to HIV (32 born infected (EI) and 36 born uninfected (EU)) and 36 unexposed and uninfected (UEUI) controls were recruited. Allelic variants (*n*=5) in the *APOBEC3G* gene were characterised.

Results. Frequencies for minor *APOBEC3G* alleles in the HIV-uninfected groups (EU and UEUI) were *c.557G* (40%), *g.-90C* (32%), *g.-571C* (12%), *c.467-85C* (42%), and *c.582-162G* (6%). *APOBEC3G c.467-85C* frequency was statistically significantly different when compared to the Masai of Kinyawa, Kenya population (42% v. 18%). None of the single nucleotide polymorphisms individually or as part of haplotypes were significantly associated with HIV infection when comparing the EI and EU groups.

Conclusions. Our findings suggest that *APOBEC3G* polymorphisms alone may not have significant predictive power for inferring genetic susceptibility to vertical transmission of HIV in children perinatally exposed to HIV.

This manuscript is written in dedication to Emeritus Professor Beighton, whom I, Collet Dandara, met in 2009. Professor Beighton has been an inspiration from whom I have always sought advice. We have co-authored two publications together and I have learnt a great deal from him, for which I am eternally grateful and indebted to him.

Background

Apolipoprotein B mRNA-editing catalytic polypeptide like-3G (*APOBEC3G*) deaminates cytidine (C) to uracil (U) in the negative strand of HIV genome and subsequently guanine (G) to adenine (A) on the positive strand leading to G to A hypermutation.[1] Hypermutated HIV genome is prone to degradation. Hypermutation also introduces multiple stop codons in the HIV reading frame, reducing viral fitness.[2] A hypermutated HIV-1 variant has reduced transmission fitness. HIV counteracts antiviral activity of *APOBEC3G* through the viral infectivity factor (Vif) targeting *APOBEC3G* for degradation.[3] *APOBEC3G* antiviral activity presents a potential therapeutic target against HIV. However, the role of polymorphisms in *APOBEC3G* on the risk of HIV infection and disease progression remains contested.

A study by An *et al.*[4] reported seven single nucleotide polymorphisms (SNPs) in *APOBEC3G*, three in the promoter, and two each in exons and introns.[4] *APOBEC3G c.557A>G* (*p.*H186R) in exon 4 is the most studied SNP and *APOBEC3G c.557G/G* genotype and *c.557G* allele have been linked to accelerated HIV disease progression compared with other *c.557A* carrying genotypes and the *c.557A* allele in adults.[4,5] In paediatric populations, the *c.557G/G* genotype has been linked to faster decline in CD4 T-cell count[6] and greater tendency to central nervous system impairment when compared with the *c.557A/A* and *c.557 A/G* genotypes.[7] However, the influence of *APOBEC3G* genetic polymorphisms in vertical transmission of HIV remains unknown.

A study measuring *APOBEC3G* mRNA levels in human cells from different groups of HIV-positive people reported that mRNA abundance followed the order: long-term non-progressors>HIV uninfected>progressors, with the mRNA levels correlating positively with CD4 T-cell counts and inversely with viral loads.[8] Kikuchi and colleagues[9] reaffirmed the importance of *APOBEC3G* activity in HIV with a demonstration of attenuation of anti-*APOBEC3G* activity of HIV-1 Vif protein in elite HIV controllers. These observations suggest that increased *APOBEC3G* expression may slow progression of disease in HIV infected individuals. Literature on *APOBEC3G* genetic polymorphisms is available for most world populations, but with very little coverage of African populations; yet, these African populations possess the most genetic diversity; thus findings from other populations may not always explain what is found in Africans. This study, therefore, describes

polymorphisms in *APOBEC3G* and their role in predicting risk of HIV infection in children by evaluating distribution of *APOBEC3G* variants in three groups of children:

- Children born to HIV-infected mother and born infected (exposed and infected, EI);
- Children born to HIV-infected mothers and born uninfected (exposed but uninfected, EUI); and
- Children born to uninfected mothers (unexposed, uninfected, UEUI). Frequencies of *APOBEC3G* variants were also compared with other African and world populations.

Methods

Study participants

A cross-sectional study of *APOBEC3G* gene polymorphisms and their possible association with HIV infection in HIV-exposed children was conducted. Participants were recruited from the Better Health for the African Mother and Child (BHAMC) cohort, a longitudinal study of mother-child pairs followed up between 2002 and 2012, as described elsewhere.[10] In summary, the participants were 104 unrelated children aged 7 to 9 years, of bantu African origin. These included 32 children perinatally infected with HIV (EI) who were available in the cohort at the time of collection, and 72 healthy HIV-uninfected children comprising 36 exposed to HIV *in utero* but not infected (EU) and 36 unexposed and uninfected (UEUI). The EU and UEUI groups were combined to form the controls. Written informed consent was obtained from each child's parent or legal guardian before the samples were collected. The study received ethics approval from the Medical Research Council of Zimbabwe and the University of Cape Town Faculty of Health Sciences Research Ethics Committee.

Genotyping of *APOBEC3G* gene variants

Genomic DNA was extracted from blood samples using the Nucleospin Blood L kit (Macherey-Nagel, Germany) according to the manufacturer's instructions. Five SNPs were investigated in the *APOBEC3G* gene; two in the promoter region (*g.-571G>C*, rs5757463 and *g.-90C>G*, rs5750743), one in exon 4 (*c.557A>G*, rs8177832) and two in introns (*c.467-85T>C*, rs3736685 and *c.582-162C>G*, rs2294367).

Variation at *c.557A>G* and *g.-90C>G* were genotyped using polymerase chain reaction-restriction fragment polymorphism (PCR-RFLP) whilst SNaPshot was used to genotype the remaining three. The *APOBEC3G* *c.557A>G* polymorphism was determined using a method previously described elsewhere but with minor modifications.[4] A 409bp DNA fragment flanking the *c.557A>G* site was generated from a PCR reaction. The PCR product was subsequently digested using 2 U of *Hha*I (Fermentas, Canada) restriction enzyme. The G allele resulted in the generation of three fragments: 194bp, 145bp and 70bp, while the A allele resulted in only two bands: 339bp and 70bp. Genotyping for *APOBEC3G* *g.-90C>G* involved amplification of a 355bp fragment flanking the SNP in a PCR reaction and digestion of the PCR products with 5 U of *Ava*I (Fermentas, Canada) to determine the allelic variants. The C variant resulted in two fragments, 259bp and 96bp whilst the G variant was undigested, presenting as a 355bp fragment.

The PCR based primer extension (SNaPshot) method was used to genotype three SNPs in the *APOBEC3G* gene; *g.-571G>C*, *c.467-85T>C* and *c.582-162C>G*. Three sets of sense and antisense primer pairs were designed to amplify three DNA fragments flanking SNPs: rs5757463G>C (Forward-GCAAATGCATCCCTTGT-GTA, Reverse-CCTCCTCTCCACCATCAAGA), rs3736685T>C

(Forward-TACCCTGACCATCTTTGTTGC, Reverse-ACA-CGAACTTGCTCCAACAGT) and rs2294367C>G (Forward-GTG-AGGCCAGGGAAGAAGA, Reverse-TGAAAGTGAATGTGG-GTGGA), respectively. Genotyping of *APOBEC3G* *g.-571G>C* and *c.582-162C>G* variants was done simultaneously in a multiplex SNaPshot reaction. The reaction contained *g.-571G>C* primer (AATTTGTAGGTCACCACGCCATAGGAACACACTACCA) and *c.582-162C>G* primer (TGGCACTGACTGTAACTAGTATC). To determine the *g.-571G>C* and *c.582-162* alleles, the SNaPshot products were analysed through capillary electrophoresis. Unlike *g.-571G>C* and *c.582-162C>G* SNPs that were genotyped in a multiplex SNaPshot, *c.467-85T>C* variants were determined in a singleplex SNaPshot, using 20 pmol of the primer (ACATCCCTTAG AATCTTGTCAGAAGAGGTTCCCACTTACTTGCTA).

Statistical analysis

Genotype and allele frequencies were calculated using Stata version 11.2 (StataCorp LP, USA) and/or SHEsisPlus online version.[11] Hardy Weinberg Equilibrium (HWE) was tested using χ^2 or Fisher's exact test with one degree of freedom. Chi-squared and Fisher's exact tests were used, where appropriate, to test homogeneity in alleles and genotypes among the participant groups. $p<0.05$ was considered statistically significant for all comparisons. Pairwise linkage disequilibrium (LD) analyses between *APOBEC3G* SNPs were carried out using SHEsisPlus and haplotypes were inferred using the expected maximisation algorithm. During inference of haplotypes, each chromosome of a homologous pair was considered individually, giving a total of two times the number ($2n$) of individuals included in the analysis.

Table 1. Demographic and clinical characteristics of study participants

Characteristics	HIV EI, *n*=32	HIV EU and UEUI, *n*=72	*p*-value
Age (years)			0.28
Mean	8.22	8.43	
SD	0.57	0.55	
Range	7.25 - 9.08	7.50 – 9.08	
Height (cm)			0.03
Mean	117.11	120.37	
SD	6.22	6.00	
Range	109 - 131	108 - 134	
Weight (kg)			0.005
Mean	20.31	22.35	
SD	1.99	3.01	
Range	17 - 34	15 - 31	
Head circumference (cm)			0.48
Mean	51.14	51.37	
SD	1.57	1.20	
Range	49 - 54	48 - 54	
Sex			
Female, *n* (%)	19 (59)	36 (50)	0.37
Male, *n* (%)	13 (41)	36 (50)	

SD = standard deviation; HIV EI = HIV exposed and infected; HIV EU = HIV exposed but uninfected; HIV UEUI = HIV unexposed and uninfected.

Results

Demographic characteristics and association of *APOBEC3G* polymorphisms with HIV infection

Demographic characteristics of participants are described elsewhere[10] and are summarised in Table 1. Table 2 shows distribution of *APOBEC3G* variants in EI and EU children and the measures of association with HIV status. The *APOBEC3G c.557G/G* (*p*.186R) genotype occurred more frequently in EI children (59%) compared with EU children (47%) but the difference was not statistically significant. None of the *APOBEC3G* variants investigated were individually associated with risk of HIV infection. Thus, haplotype analysis was carried out to evaluate effects of co-inheritance of variants on risk of HIV infection.

Haplotypes in *APOBEC3G* gene with respect to *g.-571G>C, g.-90C>G, c.467-85T>C, c.557A>G* and *c.582-162C>G* SNPs were inferred using SHEsisPlus online software. Twenty-nine HIV-infected and 64 HIV-uninfected individuals were successfully genotyped and included in haplotype and LD determination. Haplotype frequencies were compared between the HIV-infected children and HIV-uninfected. Haplotypes with frequencies less than 0.03 were excluded from analysis. Table 3 shows the haplotypes observed in HIV-infected and uninfected groups. None of the six haplotypes observed in the population was associated with risk of HIV infection in the children. *APOBEC3G* SNPs were generally in strong LD with each other except two pairs (*c.557A>G* and *c.582-162G*, D'=0.36; *c.582-162C>G* and *c.467-85T>C,* D'=0.38).

Baseline allele frequencies and their comparison with other populations

We report frequencies for minor alleles in the HIV-uninfected (EU+UEUI) Zimbabwean population: *APOBEC3G c.557G* (40%),

APOBEC3G g.-90C (32%), *APOBEC3G g.-571C* (12%), *APOBEC3G c.467-85C* (42%), and *APOBEC3G c.582-162G* (6%) (Table 4). To our knowledge, these variants are being reported for the first time in the Zimbabwean population. All SNPs conformed to the HWE in the HIV uninfected. Frequencies of variants in the current study were compared with other populations published on HapMap and National Center for Biotechnology Information (NCBI) dbSNP databases (Table 2), which include the Yoruba of Ibadan, Nigeria (YRI), African ancestry in southwest USA (ASW), Luhya in Webuye, Kenya (LWK), Maasai in Kinyawa, Kenya (MKK), Han Chinese in Beijing (HCB) and Utah residents with northern and western European ancestry (CEU). Frequencies of minor alleles in this group closely resembled those of YRI, ASW and LWK populations. *APOBEC3G c.467-85C* frequency was statistically significantly different when compared to the ASW population (42% v. 11%). The MKK genetic profile seemed to drift much more from the Zimbabwean group compared with other populations of African origin (YRI, LWK and ASW). Forty percent (*n*=2/5) of the SNPs showed significant differences between the Zimbabwean and MKK group. Asian and Caucasian populations (HCB and CEU, respectively) were largely different from the Zimbabwean population.

Discussion

This study describes genetic variation at five *APOBEC3G* loci and its association with HIV infection in Zimbabwean children born to HIV-infected mothers. The frequency of 40% for the *c.557G* allele in the Zimbabwean population is slightly higher than that observed among black South Africans (30%)[4] and African Americans (37%)[5] but much higher than observed in Caucasians (<5%)[4] and Asians (0%). The *APOBEC3G c.557A>G* polymorphism results in a significant functional effect due to the histidine to arginine (*p*.H186R) that alters *APOBEC3G*

Table 2. Frequency and distribution of *APOBEC3G* genotypes and their association with HIV status

Genotypes	HIV EI, *n* (freq)*	HIV EU, *n* (freq)	HIV UEUI, *n* (freq)	OR (95% CI)	*p*-value EI v. EU
†A3G c.557A>G (rs8177832)	*N*=32	*N*=36	*N*=36	-	-
557A/A	9 (0.28)	12 (0.33)	15 (0.42)	1.00	-
557A/G	19 (0.59)	17 (0.47)	16 (0.44)	1.63 (0.56 - 4.70)	0.32
557G/G	4 (0.13)	7 (0.19)	5 (0.14)	0.59 (0.11 - 2.66)	0.44
A3G g.-90C>G (rs5750743)	*N*=32	*N*=36	*N*=36	-	-
-90G/G	16 (0.50)	17 (0.47)	16 (0.44)	1.00	-
-90C/G	14 (0.42)	17 (0.47)	15 (0.42)	0.87 (0.30 - 2.52)	0.77
-90C/C	2 (0.06)	2 (0.06)	5 (0.14)	1.13 (0.08 - 16.50)	0.90
A3G c.467-85T>C (rs3736685)	*N*=32	*N*=36	*N*=36	-	-
c.467-85T/T	9 (0.27)	13 (0.36)	16 (0.44)	1.00	-
c.467-85T/C	19 (0.61)	16 (0.44)	15 (0.42)	1.92 (0.67 - 5.61)	0.18
c.467-85C/C	4 (0.12)	7 (0.19)	5 (0.14)	0.57 (0.11 - 2.56)	0.41
A3G c.582-162C>G (rs2294367)	*N*=31	*N*=32	*N*=34	-	-
582-162C/C	29 (0.94)	30 (0.94)	29 (0.85)	1.00	-
582-162C/G	2 (0.06)	1 (0.03)	5 (0.15)	2.07 (0.10 - 126)	0.55
582-162G/G	0 (0.00)	1 (0.03)	0 (0.00)	-	0.32
A3G g.-571G>C (rs5757463)	*N*=30	*N*=31	*N*=36	-	-
-571G/G	23 (0.77)	28 (0.90)	23 (0.64)	1.00	-
-571G/C	7 (0.23)	3 (0.10)	13 (0.36)	2.84 (0.56 - 18.63)	0.15

freq = frequency; OR = odds ratio; CI = confidence interval.
* Frequencies of genotypes were compared between EI group and EU group using the χ^2 test.
†A3G-APOBEC3G.

catalytic activity. The *c.557G* (*p.*186R) variant leads to poor protein assembly which reduces *APOBEC3G*'s catalytic function.[12] In addition to the possible effects of *p.*H186R amino acid alteration, *APOBEC3G* activity is determined by amount of enzyme available in circulation.[8] Inter-individual variation in circulating *APOBEC3G* may be a result of polymorphism in the gene's promoter and other regulatory sequences including those at exon-intron junctions or used by spliceosomes.

There is limited information on the frequency and distribution of *APOBEC3G* alleles in different populations. The frequency of the *g.*-90C allele in our study is lower than among the YRI (32% v. 44%) but higher than among Caucasians (4%). The distribution of *APOBEC3G* *c.467-85C* allele frequency was also comparable between Zimbabweans (42%) and YRI (48%) but higher than that observed among Caucasians (4%) and Asians (5%). Frequencies of *g.-571C* and *c.467-85C* alleles were generally higher among Africans compared with Caucasians. Variant *c.582-162G* allele was more frequent among Caucasians (58%) and Asians (66%) compared with Zimbabweans (6%) and YRI (4%). The distribution of *APOBEC3G* alleles *c.557G, g.-90C, c.467-85C* and *c.582-162G* in

the world mirrors distribution of HIV cases, where the highest prevalence is in sub-Saharan Africa where the highest number of HIV-infected people are found, compared with Europe and Asia. This suggests that *APOBEC3G* genetic variation may be contributing to the differences in susceptibility to HIV infection observed in different world populations. This supports findings by Skelton *et al.*[13] reporting on differential distribution of *BST-2* variants, which also mirrors HIV infection prevalence in Africa.[13]

Despite the relationship between *APOBEC3G* variants and HIV prevalence in different populations, analysis of individual *APOBEC3G* SNPs may not be a good predictor of risk of HIV infection. Our findings support observations by An *et al.*[4] who, in a multicentre study involving highly exposed seronegative and HIV-seropositive individuals, did not observe any association between *APOBEC3G* variants and HIV status. However, the *c.581+68T* allele of a *c.581+68C>T* SNP (rs17496018) in exon 4 of the *APOBEC3G* gene, which did not form part of this study, was associated with increased risk of HIV transmission.[6] These observations on *APOBEC3G* gene variation suggest that individual allelic variants may fail to show any effect on their own. However, their collective contribution to

gene expression or overall protein structure may be important, as we have shown with other genes.[10,13-15]

In an effort to understand the combinational effect of *APOBEC3G* polymorphism on HIV transmission haplotype, frequencies were compared between HIV-infected and uninfected groups of children. LD was generally strong between pairs of the *APOBEC3G* SNPs studied in the population. This conforms to studies in Argentinians, Caucasians and African Americans, where all five SNPs investigated as part of this study have been reported to be in strong LD.[4] This implies a higher likelihood of co-inheritance of these *APOBEC3G* SNPs; thus, they may collectively influence risk of HIV infection and disease progression. Nonetheless, haplotype analysis of the SNPs failed to show association with risk of HIV infection further; hence, the collective role of *APOBEC3G* polymorphisms in HIV may be negligible.

The interpretation of the effect of *APOBEC3G* genetic variation in HIV infection and disease progression is difficult due to underlying genetic factors. Polymorphisms in other APOBEC genes such as *APOBEC3F* have also been linked with differential antiretroviral activity of their protein products. Given the complex network of interaction of proteins in the cytidine deamination antiviral pathway, determination of association between *APOBEC3G* genetic variants and HIV infection or disease progression would require large sample sizes and adjusting for other proteins involved, a motivation for genome-wide association studies. Findings of this study may have been limited by the sample size, and unavailability of maternal virological and immunological information that may have influenced vertical transmission of HIV. Furthermore, the cross-sectional nature of the study makes it difficult to establish the causal relationship between *APOBEC3G* genotypes and HIV transmission. A longitudinal study using a bigger sample size and taking a pathway approach could be ideal.

Table 3. Haplotype formation with respect to SNPs on the *APOBEC3G* gene and their association with HIV status

Haplotype	HIV EI, *n* (freq)	HIV EU, *n* (freq)	Total, *n*	*p*-value
GCTAC	13 (0.224)	15 (0.250)	28	0.741
GGTAC	12 (0.206)	13 (0.216)	25	0.896
CGTAC	5 (0.086)	3 (0.050)	8	0.486
GCCGC	3 (0.051)	2 (0.033)	5	0.676
GGCGC	20 (0.344)	23 (0.383)	43	0.663
GGTAG	1 (0.017)	3 (0.050)	4	0.618
Other	4 (0.069)	1 (0.016)	5	-
Total (2*n*)	58	60	118	-

Table 4. Comparison of allele frequencies (proportions) between the HIV-uninfected (EUI+UEUI) group and other populations published on HapMap and NCBI dbSNP databases*

Minor allele	ZIM	YRI	LWK	MKK	ASW	HCB	CEU
g.-571C (rs5757463C)	0.12	0.04	NA	NA	NA	NA	0.10
c.-90C (rs5757463C)	0.32	0.44	NA	NA	NA	NA	0.32
c.467-85C (rs3736685C)	0.42	0.48	0.34	0.18[†]	0.31[‡]	0.05[†]	0.031[†]
c.557G (rs8177832G)	0.40	0.48	0.34	0.18[†]	0.31	0.05[†]	0.031[†]
c.-162G (rs2294367G)	0.06	0.04	NA	NA	NA	0.66[†]	0.523[†]

NA = not available.
* Frequencies of minor alleles for each polymorphism were compared between Zimbabweans and other populations using the χ^2 test.
[†] *p*<0.001. *P*-values are only shown where the difference from our study population was statistically significant.
[‡] *p*<0.05. *P*-values are only shown where the difference from our study population was statistically significant.

Conclusion

In conclusion, *APOBEC3G* gene is highly polymorphic in Zimbabweans, Africans and other world populations. Differences in frequencies of *APOBEC3G* variants between high HIV prevalence populations such as Africans and low-HIV populations such as Caucasians suggest the antiviral role of *APOBEC3G* enzyme may have been involved in shaping the distribution of viral diseases such as HIV. HIV infects human cells through a complex process that involves a multitude of most proteins, hence HIV disease is multifactorial. Thus, several host gene variants are likely to influence HIV pathogenesis; hence, their co-inheritance patterns present a strong candidate for determination of HIV infection and disease outcomes.

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